Professional Information for JOPAMIRON

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

JOPAMIRON 300 (50 mL) solution for injection

JOPAMIRON 300 (100 mL) solution for injection

JOPAMIRON 300 (200 mL) solution for injection

JOPAMIRON 370 (50 mL) solution for injection

JOPAMIRON 370 (100 mL) solution for injection

JOPAMIRON 370 (200 mL) solution for injection

JOPAMIRON 370 (500 mL) solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

JOPAMIRON 300: Each 1 mL contains 0,612 g iopamidol in aqueous solution.

JOPAMIRON 370: Each 1 mL contains 0,755 g iopamidol in aqueous solution.

JOPAMIRON 300:

50,0 mL solution: 30,62 g iopamidol equivalent to 15,0 g iodine.

100,0 mL solution: 61,24 g iopamidol equivalent to 30,0 g iodine.

200,0 mL solution: 122,4 g iopamidol equivalent to 60,0 g iodine.

JOPAMIRON 370:

50,0 mL solution: 37,76 g iopamidol equivalent to 18,5 g iodine.

100,0 mL solution: 75,53 g iopamidol equivalent to 37,0 g iodine.

200,0 mL solution: 151,0 g iopamidol equivalent to 74,0 g iodine.

500,0 mL solution: 377,6 g iopamidol equivalent to 185,0 g iodine.

Sugar free.

For the full list of excipients, see section 6.1.

JOPAMIRON 300:

The osmolality at 37 °C is 0,68 osm/kg H_2O.

The osmolality at 37 °C is 0,49 osm/mL solution.

JOPAMIRON 370:

The osmolality at 37 °C is 0,87 osm/kg H_2O.

The osmolality at 37 °C is 0,57 osm/L solution.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

JOPAMIRON is indicated for myelography, cisternography and ventriculography, for all angiographic and urographic examinations and for contrast enhancement in computerised tomography. Its properties also permit the visualisation of body cavities (e.g. arthrography, fistulography, vesiculography, endoscopic-retrograde cholangio-pancreaticography).

4.2 Posology and method of administration

General Information

Patients must present themselves in a fasted and adequately hydrated state on the day of the examination.

Compensation must be made for disturbances of water and electrolyte balance. This applies in particular to patients who are predisposed to such disturbances.

In the case of abdominal angiography and urography, the diagnostic yield is increased if the bowels are empty of faecal matter and gas. On the two days prior to the examination patients

should therefore avoid flatulent food, in particular peas, beans and lentils, salads, fruit, dark and fresh bread and all kinds of uncooked vegetables. On the day before the examination, patients should refrain from eating after 6 p.m. Moreover, it is appropriate to administer a laxative in the evening.

In babies, however, prolonged fasting and the administration of a laxative before the examination are contra-indicated. Calm management of the patients and appropriate premedication will obviate pronounced states of excitement, anxiety and pain-factors known to be able to cause side-effects or intensify contrast medium-induced reactions.

Sensitive patients tolerate the contrast medium better if it is warmed to body temperature, at which it is also less viscous.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the examination the patient should be kept under observation for at least 15 minutes, since the majority of all severe incidents is known to occur within this time.

After myelography - in particular in the case of myelography of upper sections - the contrast medium must always as far as possible be conducted away to the lumbar region. This is achieved by moving the patient into the upright sitting position for several minutes. Afterwards, the patient should rest in bed for at least 24 hours, with the trunk in the horizontal position and the bed head tilted up by 15 degrees.

Patients in whom it must be suspected that the stimulus threshold is reduced must be kept under careful observation for 8 hours.

At the first signs of hyperreactivity and particularly if epileptiform reactions should occur, appropriate countermeasures are to be taken (see section 4.8).

Posology

Adults and elderly

In angiography, deviations must possibly be made from the suggested dosages contained in Table 1, for adults of normal weight, depending on age, weight, cardiac output, general state of health, the clinical problem, examination technique, kind and volume of the region to be examined.

For examination of the subarachnoid region

A total iodine dose of 3 g should not be exceeded.

Paediatric population

Examinations of infants and children always require individualisation of dosages, to be chosen in the first place in relation to the region to be demonstrated, the weight and the age.

Table 1: Dosage schedule

Examination method	**Concentration of JOPAMIRON (mg iodine/mL)**	**Dosage (mL)**
Subarachnoid region		
Myeloradiculography	300	5 – 10
Cisternography and		
Ventriculography	300	3 – 10
Angiography		
Thoracic aortography	300 – 370	50 – 80
Abdominal aortography	300 – 370	50 – 80
Peripheral arteriography	300 – 370	30 – 50
Selective arteriography	300 – 370	Depending on the vessel
Phlebography	300	30 – 50
Cerebral arteriography	300	5 – 10
Angiocardiography		
Coronarography	370	8 – 15
Ventriculography	370	40 – 70
Urography		
Intravenous urography	300	50 – 100

Adults:	370	30 – 50
Children up to 8 kg body mass:	300	3 – 5 mL/kg body mass
Children over 8 kg body mass:	370	2 – 4 mL/kg body mass
	300	1 – 2 mL/kg body mass
	370	1 – 1,5 mL/kg body mass
Computerised tomography	300 – 370	0,5 – 2 mL/kg body mass

Method of administration

Intrathecal

Intraventricular

Intra-arterial

Intravenous

Intra-cisternal

Intra-articular.

4.3 Contraindications

- Hypersensitivity to iopamidol, iodine or to any of the excipients of JOPAMIRON (see section 6.1).
- Intrathecal administration: the concomitant intrathecal administration of corticosteroids with JOPAMIRON.
- Intrathecal administration: immediate repeat myelography in the event of technical failure, to avoid overdosage.
- Cerebral fits are a relative contraindication for myelography. When the examination is carried out, all facilities to counter any convulsions which may occur must first of all be made readily available (see section 4.8).
- Manifest hyperthyroidism.
- Waldenströms macroglobulinemia.
- Multiple myeloma.

- Severe kidney disease.
- JOPAMIRON should not be used during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Diagnostic procedures which involve the use of any radiopaque medium should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reaction to the contrast medium itself.

Fatal reactions have been associated with the administration of water-soluble contrast media. During the examination an intravenous route for emergency treatment in the event of a reaction is required. After the administration of the contrast medium, competent personnel, medicines and equipment for emergency resuscitation must be available for at least 30 minutes.

Caution during injection of contrast media is necessary to avoid extravasation. Local tissue irritation can occur in the case of perivascular infiltration of the contrast media.

In patients who are known epileptics or have a history of epilepsy, anticonvulsant therapy should be maintained before and following myelographic procedures. In some instances anticonvulsant therapy may be increased for 48 hours before the examination.

General information

Particular caution must be exercised in the case of hypersensitivity to iodinated contrast media. Experience shows that patients with an allergic disposition suffer more frequently from hypersensitivity reactions. In such cases some examiners administer an antihistamine or corticoid prophylactically. However, contrast media and prophylactic medicines should not be administered mixed together.

The patient should also be informed that allergic reactions may develop up to several days after the procedure; in such case, a health care provider should be consulted.

The risk of bronchospasm-inducing reactions in asthmatic patients is higher after contrast media administration, especially in patients taking beta-blockers.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed haemodynamic disturbances, which may be associated with a transitory increase in the circulating osmotic load. All other patients should be observed for at least 30 minutes after the procedure as most of the adverse events occur within this period.

Pre-existing renal impairment may predispose to acute renal dysfunction following contrast media administration. In patients with impairment of renal function, the administration of potentially nephrotoxic medicines should be avoided until the contrast medium is completely excreted. In such patients, renal function parameters should be monitored after the procedure.
In patients with impairment of renal function, the administration of potentially nephrotoxic medicines should be avoided until the contrast medium is completely excreted. In such patients, renal function parameters should be monitored after the procedure. Further administration of contrast media should be postponed until renal function has returned to its previous level.

The presence of renal damage in diabetic patients is one of the factors predisposing to renal impairment following contrast media administration. This may precipitate lactic acidosis in patients who are taking biguanides (e.g. metformin, see section 4.5). As a precaution, biguanides should be stopped 48 hours prior to the contrast medicine examination and reinstated only after control of renal function has been regained.

Patients must be sufficiently hydrated before and after radiographic procedures. Patients with severe functional impairment of the liver or myocardium, myelomatosis, diabetes, polyuria or

oliguria, hyperuricemia, infants, elderly patients and patients with severe systemic disease should not be exposed to dehydration. Fluid intake should not be limited and any abnormalities of fluid or electrolyte balance should be corrected prior to use of this hypertonic solution.
To prevent crises in patients with sickle cell disease adequate hydration should be assured and a minimal volume of low concentration should be used.

Thyroid storms have been reported following administration of iodinated contrast media to patients with, or with suspicion of, hyperthyroidism or autonomously functioning thyroid nodule(s) (see section 4.3).
It is possible that hyperthyroidism may recur in patients previously treated for Graves' disease.
Following the administration of iodinated renal contrast media, the capacity of the thyroid tissue to take up radioisotopes for diagnosing disorders of the thyroid is reduced for up to 2 weeks and even longer in individual cases after dosing with an iodinated contrast medium that is eliminated through the kidneys.
A characteristic of non-ionic contrast media is the extremely low interference with normal physiological functions. As a consequence of this, non-ionic contrast media have less anti-coagulant activity *in vitro* than ionic media. Medical personnel performing vascular catheterisation procedures should be aware of this and pay meticulous attention to the angiographic technique.

JOPAMIRON should be used with caution in patients with hypercalcaemia and cerebral vascular disease.

Vasospasm and subsequent cerebral ischemic phenomena may be caused by intra-arterial injections of contrast media.

The risk associated with a particular investigation may be increased by conditions such as advanced arteriosclerosis and hypertension.

The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis.

On intravascular administration

In patients with severe impairment of hepatic function, cardiac and circulatory insufficiency, pulmonary emphysema, poor general health, cerebral arteriosclerosis, juvenile-type diabetes or diabetes of long standing, cerebral spasmodic conditions, the need for examination merits particularly careful consideration.

Fluid intake should not be restricted before the use of JOPAMIRON in patients with juvenile-type or diabetes of long standing, polyuria, oliguria or gout or in babies, young children and marasmic patients. Compensation must be made for disturbances of water and electrolyte balance.

Patients with phaeochromocytoma can develop severe hypertensive crises following intravascular JOPAMIRON administration. Premedication with α-receptor blockers is recommended.

Contrast induced encephalopathy

Encephalopathy has been reported with the use of JOPAMIRON (see section 4.8). This may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema within minutes to hours after administration and generally resolves within days. Factors which increase blood-brain barrier permeability will ease the transfer of contrast media to brain tissue and may lead to possible CNS reactions, for instance encephalopathy. If contrast encephalopathy is suspected, JOPAMIRON should not be re-administered and appropriate medical management should be initiated.

Angiography

In patients undergoing angiocardiographic procedures special attention should be paid to the status of the right heart and pulmonary circulation. Special care should be exercised when this product is injected into the right heart or pulmonary artery in patients with pulmonary hypertension. Right heart insufficiency and pulmonary hypertension may precipitate bradycardia and systemic

hypotension, when the organic iodine solution is injected. Right heart angiography should be carried out only when absolutely indicated.

During intracardiac and/or coronary arteriography, ventricular dysrhythmias may infrequently occur.

In angiographic procedures, the possibility of dislodging plaque or damaging or perforating the vessel wall should be considered during catheter manipulation and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Angiography should be avoided whenever possible in patients with homocystinuria due to an increased risk of thrombosis and embolism.

In patients undergoing peripheral angiography, there should be pulsation in the artery into which the X-ray contrast medium will be injected. In patients with thromboangiitis obliterans or ascending infections in combination with serious ischaemia the angiography should be performed with special caution.

In paediatric roentgenology, one should proceed with great caution when injecting the contrast medium into the right heart chambers of cyanotic neonates with pulmonary hypertension and impaired cardiac function.

In examinations of the aortic arch the tip of the catheter should be positioned carefully to avoid hypotension, bradycardia and central nervous system (CNS) injury due to excess pressure transmitted from the injector pump to the brachiocephalic branches of the aorta.

Likewise, in abdominal aortography, excess pressure from the pump may cause renal infarction, spinal cord injury, retroperitoneal bleeding, intestinal infarction and necrosis. In peripheral arteriography JOPAMIRON 370 may sometimes cause a painful reaction in the involved limb. This is usually not the case with the less concentrated solution JOPAMIRON 300.

In patients undergoing venography, special caution should be exercised in patients with suspected phlebitis, serious ischaemia, local infections, or a complete venous occlusion.

JOPAMIRON should be administered with caution in patients with symptomatic cerebrovascular diseases, recent stroke, or frequent transient ischemic attack (TIA), altered permeability of the blood-brain barrier, increased intracranial pressure, suspicion of intracranial tumour, abscess or haematoma/haemorrhage, history of convulsive disorder or alcoholism.

Neuroradiology

The contrast medium should be removed as much as possible in case of spinal fluid blockage.
Anticonvulsant therapy should be maintained before and following myelographic procedures in patients who are known to suffer from convulsions.
If during the procedure a convulsive crisis occurs, it is recommended to administer intravenously diazepam or phenobarbital (phenobarbitone).
Neuroleptics must be absolutely avoided, because they lower the seizure threshold. The same applies to analgesics, anti-emetics, antihistamines and sedatives of the phenothiazine group.
Whenever possible, treatment with medicines should be discontinued at least 48 hours before administration of the contrast medium and not be resumed less than 12 hours after completion of the procedure, particularly in thoracic and cervical myelography and in ventriculography.
Caution must also be exercised in alcoholics and drug addicts because of the possibility of a reduced stimulus threshold.

Intrathecal administration

If from clinical history, there is a previous history of epilepsy or in the presence of blood in the cerebrospinal fluid or presence of local or systemic infection where bacteraemia is likely, special caution for use of JOPAMIRON is advised.
After completion of direct cervical or lumbo-cervical procedures:

- Raise head of table steeply (45 degree angle) for about two minutes so that the contrast medium flows towards the caudal end.
- Avoid excessive and particularly active patient movement or straining, maintain the patient under close observation, quiet and in a head up position especially in the first few hours.

The patient should remain supine and at bed rest during this period. Encourage the patient, if able, to take in fluids orally and eat.

Urography

Care should be exercised in patients with moderate impairment of renal function (as reflected by a raised blood urea). Substantial deterioration in renal function is minimised if the patient is well hydrated. Renal function parameters, especially urinary output, should be monitored after the examination in these patients.

Re-examination should be delayed for 5 to 7 days.

Hypersensitivity

With JOPAMIRON as with any other iodinated contrast medium, the possibility cannot be ruled out that – irrespective of the amount and the type of contrast medium administered – individual patients will react particularly sensitively to such compounds.

Contrast media products may provoke anaphylaxis or other manifestations of allergy with nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. Occasional severe reactions with fatal outcome have been reported.

The investigation must be interrupted if more pronounced side effects or reactions of allergy occur during the administration. If, despite this, the reactions do not disappear, or even grow worse, the investigation must be terminated. However, the cannula or catheter must be left in the vessel ready for any therapeutic measures. Even minor symptoms, such as itching of the skin, sneezing, violent yawning, tickling in the throat, hoarseness and coughing fits, may be initial signs of a severe reaction (including shock), so careful attention should be paid to them. Some examiners administer an antihistamine or corticoid prophylactically. Experienced radiologists are of the opinion that the best precautions that can be taken against the contrast medium incidents are to have immediately available relevant therapeutic aids, including appropriate medicines (e.g. adrenaline), an endotracheal tube and a respirator (see section 4.8).

Suggestions for the management of life-threatening acute hypersensitivity reactions or acute anaphylaxis after administration of contrast media.

Give adrenaline solution 1 mL of 1:1000 concentration (1 mg) subcutaneously. Repeat if necessary 5 to 10 minutes later. If the patient does not respond immediately give 0,1 to 0,4 mL of 1:1000 concentration diluted in 10 mL physiological saline intravenously slowly.

Maintain an open airway. An emergency tracheotomy may be necessary. Positive pressure oxygen administration may be required.

In the event of urticaria or angio-oedema, administer adrenaline subcutaneously followed by an antihistamine intravenously (e.g. diphenhydramine hydrochloride 20 mg).

For prolonged or severe reactions give hydrocortisone sodium succinate 250 mg or methylprednisolone sodium succinate 100 mg intravenously over 30 seconds after adrenaline and the antihistamine.

Aminophylline injection 250 to 500 mg should be given slowly intravenously in the presence of bronchospasm.

Intravenous fluids may be required to correct hypovolaemia.

Special Populations

Elderly

The elderly are at special risk of reactions due to reduced physiological functions, especially when high dosage of contrast medium is used. Myocardial ischemia, major dysrhythmias and premature ventricular complexes are more likely to occur in these patients. The probability of acute renal insufficiency is higher in these patients.

Paediatric population

Infants (aged < 1 year) and especially new-borns are particularly susceptible to electrolyte imbalances and haemodynamic alterations. Care should be taken regarding the dosage to be used, the details of the procedure and the patient's status. Great caution should be paid when injecting the contrast medium into the heart chambers, especially in cyanotic neonates with

pulmonary hypertension and impaired cardiac function.

Transient thyroid suppression or hypothyroidism has been observed in children after exposure to iodinated contrast media.

Following a diagnostic procedure, this has been more frequently observed in neonates and premature infants and also following procedures associated with higher doses. Neonates may also be exposed via maternal exposure. In neonates, especially preterm infants, who have been exposed to JOPAMIRON, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function. If hypothyroidism is detected, thyroid function should be monitored until normalised.

4.5 Interaction with other medicines and other forms of interaction

Thyroid function tests: JOPAMIRON may interfere with tests for thyroid function. Following administration of JOPAMIRON, the capacity of the thyroid tissue to take up iodine is reduced for 2 – 6 weeks. Following administration of JOPAMIRON atypical adverse reactions e.g. erythema, fever and flu symptoms have been reported in patients treated with interleukin-2.

To prevent onset of lactic acidosis in diabetic patients under treatment with oral anti-diabetic medicines of the biguanide class and with moderate renal impairment undergoing elective procedures, biguanides should be stopped 48 hours prior to the administration of the contrast medium and re-instated only after 48 hours if serum creatinine is unchanged (see section 4.4).

In emergency patients in whom renal function is either impaired or unknown, it is recommended that metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

Patients with normal renal function can continue to take metformin normally.

Cardiac and/or hypertensive patients under treatment with diuretics, ACE-inhibitors and/or beta-blocking medicines are at higher risk of adverse reactions when administered iodinated contrast media.

Beta-blockers may impair the response to treatment of bronchospasm induced by contrast medium.

In patients receiving beta-blockers there is an elevated risk of more severe anaphylactoid reactions.

Arterial thrombosis has been reported when JOPAMIRON was given following papaverine.

The administration of vasopressors strongly potentiates the neurological effects of intra-arterial contrast media.

Contrast media may interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should not be assayed during the same day following the administration of contrast media.

Intrathecal administration

Neuroleptics should be avoided as they lower the seizure threshold. This is also true for medicines such as analgesics, antiemetics, antihistamines, or sedatives of the phenothiazine group.

Wherever possible the therapy with such medicines must be discontinued at least 48 hours before the radiological investigation and treatment can be resumed not earlier than 24 hours afterwards.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Appropriate investigations and measures should be taken when exposing women of child-bearing potential to any X-ray examination, whether with or without contrast medium.

X-ray examination of women should, if possible be conducted during the pre-ovulation phase of the menstrual cycle.

Pregnancy

JOPAMIRON should not be used during pregnancy (see section 4.3). The safety of JOPAMIRON in pregnancy has not been established. Where possible, exposure to radiation should be avoided during pregnancy.

Breastfeeding

Iodine-containing X-ray contrast medicines are excreted into the breast milk in low amounts. From animal experience, JOPAMIRON is non-toxic in animals after oral administration. From experience gained so far, harm to the nursing infant is unlikely to occur. Stopping breastfeeding is unnecessary.

Fertility

No data on male and female fertility are available.

4.7 Effects on ability to drive and use machines

There is no known effect on the ability to drive and operate machines. However, because of the risk of early reactions, driving or operating machinery is not advisable for one hour following the last intravascular injection. Driving or operating machinery is not advisable for 6 hours following intrathecal administration.

4.8 Undesirable effects

Skin reactions may occur in the form of various types of rash or diffuse blister formation.
Side effects are usually mild to moderate and transient in nature; however, rare severe and life-threatening reactions, sometimes leading to death, have been reported.

Following intravascular administration, in most cases reactions occur within minutes of dosage. However, delayed reactions, usually involving skin, may occur, mostly within 2 – 3 days, more

rarely within 7 days, after the administration of the contrast medium.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with JOPAMIRON administration (see section 4.4).

After intrathecal administration, most side effects occur with a delay of some hours due to the slow absorption from the site of administration and distribution to the whole body. Reactions usually occur within 24 hours after injection.

4.8.1 Intravascular administration

Tabulated summary of adverse reactions

The following terminologies have been used in order to classify the occurrence of adverse reactions: very common (≥ 1 / 10); common (≥ 1 / 100 to < 1 / 10); uncommon (≥ 1 / 1 000 to, < 1 / 100); rare (≥ 1 / 10 000 to < 1 / 1 000); very rare (< 1 / 10 000), not known (cannot be estimated from the available data).

System organ class	**Adverse reactions**	**Adverse reactions**	**Adverse reactions**
	Frequency: Common	**Frequency: Uncommon**	**Frequency: Rare**
Psychiatric disorders			Confusional state
Nervous system disorders	Headache	Dizziness, taste alteration	Paraesthesia
Cardiac disorders		Cardiac dysrhythmias such as extrasystoles, atrial fibrillation, ventricular tachycardia and ventricular fibrillation*	Bradycardia
Vascular disorders		Hypotension,	

		hypertension, flushing	
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema, asthma, bronchospasm
Gastrointestinal disorders	Nausea	Vomiting, diarrhoea, abdominal pain, dry mouth	
Skin and subcutaneous tissue disorders		Rash, urticaria, pruritus, widespread erythema, increased sweating	
Musculoskeletal and connective tissue disorders		Back pain	Muscle spasms
Renal and urinary disorders		Acute renal failure	
General disorders and administration site conditions	Generalised heat sensation /feeling hot	Chest pain, injection site pain, fever/pyrexia, feeling cold	
Investigations		Increased blood creatinine	

Post-marketing surveillance

The following post-marketing experiences have been reported after intravascular administration:

Blood and lymphatic system disorders: Thrombocytopenia.

Immune system disorders: Anaphylaxis, anaphylactoid reaction.

Nervous system disorders: Coma, transient ischaemic attack, syncope, depressed level of

consciousness or loss of consciousness, convulsion, hemiplegia, contrast induced encephalopathy**.

Eye disorders: Transient blindness, visual disturbance, conjunctivitis, photophobia.

Cardiac disorders: Myocardial ischaemia or infarction, cardiac failure, cardio-respiratory arrest, tachycardia, Kounis syndrome.

Vascular disorders: Circulatory collapse or shock.

Respiratory, thoracic and mediastinal disorders: Respiratory arrest, respiratory failure, acute respiratory distress syndrome, respiratory distress, apnoea, laryngeal oedema, dyspnoea.

Gastrointestinal disorders: Salivary hypersecretion, salivary gland enlargement.

Skin and subcutaneous tissue disorders: Laryngeal or face oedema, acute generalised exanthematous pustulosis (AGEP).

Musculoskeletal and connective tissue disorders: Musculoskeletal pain, asthenia/muscular weakness.

General disorders and administration site conditions: Malaise, rigors, pain.

Investigations: Electrocardiogram change including ST segment depression.

* Cardiac dysrhythmias may occur mostly after cardiac angiographic and coronary catheterisation procedures.

** Contrast induced encephalopathy may manifest with symptoms and signs described in section 4.4.

Description of selected adverse reactions

Local complaints such as sensations of heat or pain may occur but, like occasional nausea, they disappear again quickly after administration.

Coronary artery thrombosis has been reported as a complication of coronary catheterisation procedures.

Other cardiac reactions which may occur as a consequence of the procedural hazard include

coronary artery dissection.

Anaphylaxis (anaphylactoid reactions/hypersensitivity) may manifest with mild localised or more diffuse angioneurotic oedema, tongue oedema, laryngospasm or laryngeal oedema, dysphagia, pharyngitis and throat tightness, pharyngolaryngeal pain, cough, conjunctivitis, rhinitis, sneezing, feeling hot, increased sweating, asthenia, dizziness, pallor, dyspnoea, wheezing, bronchospasm and moderate hypotension. Skin reactions may occur in the form of various types of rashes, diffuse erythema, diffuse blisters, urticaria and pruritus. These reactions, which occur irrespective of the dose administered and the route of administration, may represent the first signs of incipient state of shock. Administration of the contrast medium must be discontinued immediately and if necessary, specific treatment initiated via a venous access.

More severe reactions involving the cardiovascular system such as vasodilatation with pronounced hypotension, tachycardia, dyspnoea, agitation, cyanosis and loss of consciousness progressing to respiratory and/or cardiac arrest may result in death. These events can occur rapidly and require full and aggressive cardio-pulmonary resuscitation.

Primary circulatory collapse can occur as the only and/or initial presentation without respiratory symptoms or without other signs or symptoms outlined above.
Injection site pain and swelling may occur. On very rare occasions extravasation of contrast medium led to inflammation (manifested with local erythema, oedema and blisters), skin necrosis and compartment syndrome.
Very rare cases of mucocutaneous syndromes, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome) and erythema multiforme, have been reported following the administration of JOPAMIRON.

Paediatric patients

The JOPAMIRON safety profile is similar in children and adults. Cases of transient neonatal

hypothyroidism have been reported with JOPAMIRON in very low birth weight infants.

4.8.2 Intrathecal administration

Tabulated summary of adverse reactions

The following terminologies have been used in order to classify the occurrence of adverse reactions: very common (≥1 / 10); common (≥ 1 / 100 to < 1 / 10); uncommon (≥ 1 / 1 000 to, < 1 / 100); rare (≥ 1 / 10 000 to < 1 / 1 000); very rare (< 1 / 10 000), not known (cannot be estimated from the available data).

System organ class	**Adverse reactions**	**Adverse reactions**	**Adverse reactions**
	Frequency: Common	**Frequency: Uncommon**	**Frequency: Rare**
Nervous system disorders	Headache		
Vascular disorders		Flushing	
Gastrointestinal disorders		Nausea, vomiting	
Skin and subcutaneous tissue disorders			Rash
Musculoskeletal and connective tissue disorders		Back pain, neck pain, pain in extremity, sensation of heaviness.	

Post-marketing experience

The following post-marketing experiences have been reported after intrathecal administration:

Infections and infestations: Aseptic meningitis, bacterial meningitis as consequence of the

procedural hazard.

Immune system disorders: Anaphylaxis, anaphylactoid reaction.

Psychiatric disorders: Confusional state, disorientation, agitation, restlessness.

Nervous system disorders: Coma, paralysis, convulsion, syncope, depressed level of consciousness or loss of consciousness, meningism, dizziness, paraesthesia, hypoaesthesia, contrast induced encephalopathy, transient ischaemic attack, hemiplegia, contrast induced encephalopathy*.

Eye disorders: Transient blindness.

Cardiac disorders: Dysrhythmia.

Vascular disorders: Hypertension.

Respiratory, thoracic and mediastinal disorders: Respiratory arrest, dyspnoea.

General disorders and administration site conditions: Pyrexia, malaise, rigors.

* Contrast induced encephalopathy may manifest with symptoms and signs described in section 4.4.

Description of selected adverse reactions

Anaphylaxis (anaphylactoid reactions/hypersensitivity) may occur. Anaphylactoid reactions with circulatory disturbances such as severe blood pressure decrease leading to syncope or cardiac arrest and life-threatening shock are much less common after intrathecal administration than after intravascular administration. Also, less common than after intravascular administration are the respiratory (dyspnoea or respiratory distress in the form of bronchospasm) and mucocutaneous manifestations (urticaria, angioneurotic oedema and other skin reactions like rash).

The most common subjective complaints are nausea, vomiting and headache. However, headaches are no more frequent than after the loss of pressure in the subarachnoid space caused by lumbar puncture. In view of this, an effort should be made to remove only as much fluid as is being replaced by the JOPAMIRON solution. On the other hand, administration of an amount of

contrast medium in excess of the amount of fluid removed does not lead to an increase of pressure in the subarachnoid space.

Seizures have been reported with the use of JOPAMIRON in myelography.

Severe headaches lasting several days may occur. Examinations of the thoracic and cervical regions are attended by a higher incidence of headaches, nausea and vomiting than are examinations of the lumbar region. The possible reasons for this are the higher dose and the increased risk of undiluted contrast material entering the intracranial spaces as a result of undesired movements by the patient or of keeping the patient in the head-down position for too long. If penetration of undiluted contrast material into the basal systems is assumed, administration of 0,2 g phenobarbital (phenobarbitone) i.m. is advised as a prophylactic measure against epileptiform reactions. If convulsions occur, 10 mg diazepam must be administered immediately as a slow i.v. injection, followed 20 to 30 minutes after subsidence of the convulsions - unless it has already been given prophylactically – by 0,2 g phenobarbital (phenobarbitone) i.m. to prevent recurrence. Mainly because of its rapid onset of action, diazepam should be injected i.v. as a precaution at the first signs of hyperreactivity or muscular twitching.

Minor side effects are drowsiness, pain or intensification of existing pain in the back, nape and extremities.

Transient states of confusion, hallucinations and non-specific temporary EEG changes may occur in isolated cases.

Relatively slight muscular tension, paresis and paraesthesia have been observed 2 to 6 hours after the injection.

Administration of 0,2 mg phenobarbital (phenobarbitone) i.m. is recommended in restless states or headache.

Paediatric patients

The JOPAMIRON safety profile is similar in children and adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of JOPAMIRON is important. It allows continued monitoring of the benefit/risk balance of JOPAMIRON. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (whoumc.org) found on SAHPRA website.

4.9 Overdose

Symptoms of overdosage

Dosages exceeding the specific package insert dose are not recommended, as they might lead to life-threatening adverse effects.

With overdosage, the symptoms described under section 4.8 may occur, which should be treated according to the recommended procedures to be adopted in incidents after the administration of contrast media.

If needed, haemodialysis can be used to eliminate JOPAMIRON from the body.

Treatment of overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Intravascular

In the event of accidental intravascular overdose in humans, the water and electrolyte losses must be compensated by infusion.

Renal function should be monitored for at least three days.

Intrathecal

Signs of intrathecal overdose may be ascending hyperreflexia or tonic-clonic spasms, up to generalised seizures and in severe cases of central involvement, hyperthermia, stupor and respiratory depression.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 28. Contrast media.

Pharmacotherapeutic group: Water-soluble, nephrotropic, low osmolar X-ray contrast media.

ATC code: V08AB04.

Iopamidol is contrast medium belonging to the class of non-ionic compounds whose solubility is due to the presence of hydrophilic substitutes in the molecule. This results in a solution of low osmolality when compared with ionic media.

5.2 Pharmacokinetic properties

The pharmacokinetics of iopamidol conforms to an open two compartment pharmacokinetic model with first order elimination.

Following intravenous administration, iopamidol is excreted rapidly and almost entirely by the kidneys, with less than 1 % of the administered dose has been recovered in the faeces up to 72 hours after dosing. Elimination is rapid; up to half the administered dose may be recovered in the urine in the first two hours of dosing. Serum protein binding is negligible. Distribution volume is equivalent to extracellular fluid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium disodium edetate (dihydrate)

Trometamol

Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

60 months.

Once opened, use immediately.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light, heat and secondary X-rays.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Colourless glass bottle.

Pack sizes:

JOPAMIRON 300: Bottles of 50 mL, 100 mL and 200 mL.

JOPAMIRON 370: Bottles of 50 mL, 100 mL, 200 mL and 500 mL.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Any contrast medium solution left over from the examination must be discarded. In rare cases, crystals may form in the highly concentrated solution of JOPAMIRON even before the ampoule or bottle is opened. It has been shown that such a phenomenon is caused by a damaged or defective container. Do not use solutions in which this change has taken place.

JOPAMIRON, as other iodinated contrast media, can react with metallic surfaces containing copper (e.g. brass). Therefore, the use of equipment in which JOPAMIRON comes into direct contact with such surfaces, should be avoided.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AXIM PHARMACEUTICALS (Pty) Ltd

63 Old Pretoria Main Road

Halfway House 1685

Midrand, South Africa

Tel: +27 11 314 0140

8. REGISTRATION NUMBERS

JOPAMIRON 300 (50 mL): Q/28/202

JOPAMIRON 300 (100 mL): Q/28/203

JOPAMIRON 300 (200 mL): 59/28/0229

JOPAMIRON 370 (50 mL): Q/28/205

JOPAMIRON 370 (100 mL): Q/28/206

JOPAMIRON 370 (200 mL): 59/28/0230

JOPAMIRON 370 (500 mL): 59/28/0231

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

JOPAMIRON 300 (50 mL): 22 July 1983

JOPAMIRON 300 (100 mL): 22 July 1983

JOPAMIRON 300 (200 mL): 25 November 2025

JOPAMIRON 370 (50 mL): 22 July 1983

JOPAMIRON 370 (100 mL): 22 July 1983

JOPAMIRON 370 (200 mL): 25 November 2025

JOPAMIRON 370 (500 mL): 25 November 2025

10. DATE OF REVISION OF THE TEXT

To be allocated.